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Image-guided therapy: evolution and breakthrough

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Beyond the advances made in computer-assisted interventions and robotic systems [1], the demand of more efficient and safer therapies remains challenging. Thus, if it is possible today to improve the instrument tracking and steering, the target localization, to miniaturize the sensors and actuators and to conduct preoperatively planned minimally invasive therapies, we still need new resources to achieve permanent destruction of abnormal tissues or suppression of pathological processes. Most of the physics-based (or energy-based) therapeutic principles at our disposal have been established a long time ago but their actions on basic cellular and molecular mechanisms are not yet fully understood. They all have a wide spectrum of clinical targets in terms of organs and pathologies, modes of application (external, interstitial, intraluminal, etc.) with advantages and side-effect drawbacks, proven indications and contraindications. Some of them may still face controversies regarding their outcomes. This short paper, mainly focused on tumor destruction, briefly reviews in its first part some of these techniques and sketches the next generation under investigation. The former include radiofrequency (RF), high intensity focused ultrasound (HiFU), microwaves and cryotherapy, all being temperature-based. Laser-based approaches (e.g. photodynamic therapy at large) are also discussed. Radiotherapy and its variants (hadrontherapy, brachytherapy, Gamma knife and Cyberknife) remain of course the reference technique in cancer treatment. The next breakthroughs are examined in the second part of the paper. They are based on the close association between imaging agents, drugs and some stimulation technique. The on-going research efforts in that direction show that, if they are still far from clinical applications, strong expectations are made. From the point of view of interventional planning and image guidance, all of them share a lot of concerns.

Improving current therapies

Hyper- and hypothermia exposures and radiotherapy treatments are aimed at tissue destruction. Although complex, the latter has well-established protocols while the former still needs guidelines to set the conditions for thermal damage in humans. They have been successful for localized tumors through extracorporeal, interstitial or endocavitary uses. Imaging guidance is required in order to target the tumor site and to monitor the treatment intra-operatively either by independent imaging modalities or by a stand-alone dual-mode device integrating imaging and therapeutic capabilities. Imaging objectives and constraints depend on multiple factors such as the targeted organs, access paths, and therapeutic process. Furthermore, not only energy deposition has to be concentrated on the target while minimizing its impact on surrounding tissues and organs as for radiotherapy but it depends on multiple parameters to be adjusted and a precise real-time measure of temperature must be available.

Temperature-based therapies

Radiofrequency ablation (RFA) is based on electric current-mediated heat applied through an electrode placed into the target. Resistive heating around the RFA electrode is produced by fast ion oscillations at frequency typically ranging over 450-500 kHz [2] [3]. In order to avoid different sequential placements into large lesions, multitined electrodes (figure 1) or internal electrode cooling is sometimes used. Monopolar and bipolar energy delivery are also considered. The surrounding tissue temperature can be directly controlled by sensors located in the tips of the electrodes or by measuring the tissue impedance. Atrial fibrillation suppression is a major application of this thermoablative technique but applications for unresectable cancer increase significantly within the last years. RFA has the advantage of small diameter probes but requires 10-25 minutes for treatment.

Microwave ablation (MWA) is obtained by creating rapid oscillations of water molecules, thus causing frictional heating leading to coagulation and necrosis. MWA probes are basically coaxial waveguides [4]. Several frequencies, 915 MHz and 2.45 GHz, are authorized and lead to treat volumes up to 4-5 cm in diameter. Improvements in antenna design (from triaxial to dielectric resonator antenna) have been recently brought with the objective to extend the treated area, to better conform the radiation pattern and to reduce the probe size. MWA is considered as less affected by the heat sink problem due to the presence of large vessels nearby the tumor as compared with RFA and HiFU. Shorter ablation times are achieved but minimizing the probe diameter currently reaching a few centimeters remains challenging.

High intensity ultrasound has raised a lot of interest for years [5] and is now widely disseminated. Focused transducers, *HiFU* (High Intensity Focused Ultrasound) and non (or weakly) focused transducers, *HiCU* (High Intensity Contact Ultrasound), operating at a few MHz, are marketed (figure 2). They incorporate ultrasound imaging sensors for guidance. The energy delivered over a few seconds can induce high temperatures (typically $>60^{\circ}\text{C}$) and generate irreversible tissue necrosis at the target region while not damaging surrounding tissues. An active research is conducted in this field and major improvements can be expected for a full electronic 3D phased array focusing and miniaturized probes allowing interstitial procedures. Today assessed for prostate cancer treatment, they should find a wide spectrum of clinical applications. The main technical limitation remains however the time required (e.g. few hours) to ablate tumors of large diameters. Another major step is under progress with the CMUT (Capacitive Micromachined Ultrasound Transducers) technology [6] which may offer better performance in pressure field, bandpass and more flexibility in probe topology design than the current piezoelectric technology.

Laser ablation, e.g. laser-induced thermotherapy, is another approach with a large range of clinical applications. Light in the near infrared part of the spectrum -- as from a NdYAG laser at 1064 nm or a semiconductor diode laser at 805 nm -- can be effective up to 10 mm of tissue. Beams are transmitted via thin fibers, so that endoscopic procedures can be applied, and focused to small spots to destroy tissues. Interstitial laser photocoagulation can be performed over a few minutes via fibers through needles at low power (about 3 W, avoiding so tissue vaporization, to be compared with the 60-80 W used endoscopically). Low level laser (LLLT) [7] is also expected for improving wound healing, repair of soft tissues and relief of pain and inflammation. However, like all the physical therapies described here, the key issues rely on a precise positioning the fibers in the target area, the control of the extent of laser induced necrosis to the tumor volume, therefore, image-guidance is here critical too.

Cryotherapy consists to locally induce very cold temperatures (-75°C) at a catheter tip below -75°C which results in irreversible cell destruction within a so-called “ice ball”. The adhesion of the tip to the tissue leads to a stable ablation [2] [8]. A recent breakthrough has been made by the introduction of argon gas rather than liquid nitrogen. Argon, taking advantage of the Joule-Thompson effect, provides a faster cooling of the cryoprobe (figure 3) which significantly speeds up the treatment and makes easier the sequential control of freeze-thaw cycles (thawing is achieved by helium). Multiple cryoprobes, each with embedded thermocouple for temperature monitoring, allow for large tumor ablation as in liver. Although this technology evolved significantly the last few years, and can now be performed percutaneously with smaller probes facilitating their placement, it is often replaced by RF treatment.

Radiation therapy

Conventional radiotherapy with photon beams (X-rays) is the main technique and the gold standard reference for cancer treatment. Significant steps forward have been made in the 60's and 70's in medical imaging and the new capabilities offered in 3D visualization of the anatomical structures that allowed to better plan and compute radiation dose by taking into account the different tissue attenuations. Advances have also been seen with *3D-conformal* and *intensity modulated radiation therapies* (IMRT) in order to limit the irradiation of healthy tissues, the main concern of all physical therapies as we have seen before. By conforming the dose to the target shape, a higher concentration can be achieved while minimizing the impact on the selected normal tissues. IMRT makes use of 6-10 beams, coplanar or non-coplanar, their intensity being varied across the irradiation field by means of computer controlled collimators (“multileaf collimators”). Conformal dose distribution can be improved through recent advanced techniques such as Volumetric Modulated Arc Therapy (VMAT) where the target is continuously irradiated while the source of the beam is rotated around the patient in single or multiple arcs. Sophisticated simulation planning programs (e.g. inverse problem) have been or have still to be developed to optimize the dose delivery. External beam therapy includes Gamma knife and more recently the fully robotized Cyber knife. Hadrontherapy is a new technique, also external, based on non-elementary particles. However, an alternative is represented by brachytherapy (also known as curietherapy) where radioactive sources are placed inside or near the area to be treated.

Brachytherapy has been considered effective for very different situations (prostate cancer for instance). This modality is one of the oldest [9], which may be either temporary or permanent. In temporary brachytherapy, the radioactive sources are placed inside or near a tumor for a specific amount of time and then withdrawn. Permanent low dose brachytherapy (also called “seed” implantation) involves placing radioactive seeds in or near the tumor and leaving them until their radioactivity goes to zero (several weeks or months according to the type of used radioactive sources). A pre-operative planning, image-based, is required in order to find the optimal locations and the amount of time needed to deliver the correct radiation dose. An accurate, intra-operative positioning of the sources in patient's body has to be achieved for a successful therapy. The assumption made here is that the radioactive seeds will not shift during the overall treatment period.

Gamma Knife can be seen as an advanced step in focused multibeam radiation therapy (for a recent review of other radiosurgery systems, X-knife, CyberKnife (figure 4), etc. refer to [10]). Originally proposed by the Swedish neurosurgeon Lars Leksell for neurosurgery, Gamma Knife is a self-contained unit with 201 Cobalt-60 sources mounted in a hemispheric array

(figure 5) such that gamma ray beams focus to a common point (isocenter). Multiple isocenters are used to match the global radiation dose distribution to an irregular tumor volume. Its interchangeable collimating helmets allow variation of focusing point size, exposing the desired beam diameter such as 4, 8, 14, and 18 mm. An alternative is the Rotational Gamma System with 30 Colbat-60 sources arranged in a rotating hemispheric shell [11], simulating an infinite number of beams and promoting extremely high target to surface dose ratios. Its collimating system is a concentric collimating hemisphere, inside the source hemisphere, co-rotating with the sources, to achieve the same desired beam diameters as Gamma Knife. Treatment planning (figure 6) is a key subsystem of Gamma Knife, which includes the functionality required to import patient images, calculate dose distributions, simulate and evaluate treatment plans, verify treatment parameters, and export completed plans to the treatment unit.

Hadrontherapy (or charged particle therapy) exploits heavy protons and has the advantage over photons or lighter particles to penetrate deeply in the body while transferring almost all the energy at the end of their path., the peak dose known as the “Bragg Peak”, allowing thus to reduce the dose to the healthy tissues in front [12]. The position of this sharp peak depends on the mass and the speed of the particles. Thus, the depth can be controlled by varying the beam energy and a homogeneous dose delivered over the whole volume of interest by spreading out the Bragg Peak. Heavy ions, such as carbon, have a higher relative biologic effectiveness (RBE) than protons and are expected to offer more efficient treatment for deep-seated tumors. The beam produced by a cyclotron or synchrotron is narrow (4-10 mm diameter) and is enlarged by passive scattering or active directional scanning (using magnetic fields in such a way that a point-based treatment, intensity modulated, is carried out over the target volume). Technically very sound and appealing by its principles, proton therapy has not yet demonstrated significant benefits and carbon ion therapy must still be considered as experimental. Much more clinical evidence is required according to the high costs involved by this technology.

Multimodal therapy

As pointed out above, both basic research is required to better understand the physical effects of temperature-based therapies on normal and abnormal tissues, and more clinical, multi-centre and comparative trials are needed. Most of them are today combined with radiotherapy techniques leading to the concept of “multimodal therapy”. The motivations can be to make use either of their different advantages and effects, or to face a failure of the first applied therapy (evidence supports the consideration of cryotherapy and HiFU after external-beam radiotherapy, for instance). The multimodal therapy is similar to that known in medical imaging for a while. In such case, registration issues, so fundamental in medical robotics, are of concern. As with any other treatment for cancer, appropriate patient selection is critical and determines the outcome.

New perspectives for computer-assisted interventions are open when temperature-based approaches are applied. Emphasis is put in the literature on the need to design well defined planning which is of course of major importance. More critical and challenging in our point of view is the adaptive way required to manage the treatment. Ideally, the temperature must be not only measured but also controlled in real-time and heat and cooling adjusted accordingly. This means to be capable to solve the heat equation for instance (the tissue is heterogeneous and vessels play an important role in modifying the boundary conditions) and consequently update the treatment plans while the temperature is continuously evolving. This is a very

challenging task. The temperature measurement can be available either directly when sensors are put on the catheter tip or indirectly through MRI. In the latter case, if additional interventional constraints and costs must be taken into account, the high demand in other clinical applications for the development of MRI compatible robotic systems should be an advantage. High Intensity Ultrasound technique, although still mainly used in a stand-alone station, is already concerned. Apart the measure, the benefit is also to access to fully 3D data providing reliable and precise positions of the target and the probe.

Physically-enhanced and image-guided drug therapy

Beyond the above physical therapies, new approaches are on the way. Drug delivery activated by heat, ultrasound or light belongs to these new attempts. Several factors in fact limit the molecular target therapies among which the high fluid pressure, the balance to make between delivery, determined by perfusion, and accumulation, resulting from permeability. The molecular size of the agent has of course also a major role. The first way to improve this process consists to modify the drug in order to facilitate the accumulation at the target site. It may be performed for instance by adding a carrier vehicle encapsulating the molecule (liposomes, nanoparticles or polymers). An alternative is to modify the physiological conditions of the tumor in order to decrease its resistance to accumulation and increase the perfusion. Dual monitoring low hyperthermia and drug deposit for this purpose is a sound and challenging way to do that. If some imaging agent (e.g. probe) is added, tracking the delivery becomes effective.

In short, five components represented by a chemotherapeutic drug, a drug delivery vehicle, an imaging agent suited for MRI, PET, ultrasound, optical imaging, etc. together with an appropriate activation mean, define the next breakthrough to be accomplished. Radiofrequency, microwave, ultrasound and light are of interest to boost and control intracellular drug delivery. The major impact on cancer treatment that can be expected explains the many studies presently conducted on thermosensitive liposomes for example.

Microbubble carriers are a way to deliver drugs and therapeutic genes. Acoustically-driven active lipospheres (AALs) are used by Ferrara [13] and when these microbubbles are in place, they are fragmented by higher intensity ultrasound, spraying their contents into the target tissue. Although focused by now on liposphere delivery to blood vessel walls, this principle should have broad applications. The combination of imaging function, release and radiation force, with different frequency bands, in a unique transducer could open major clinical windows.

Light activated treatment has also a great potential although no applications have not yet fully established. This *photodynamic therapy* (PDT), a cheap therapy, provides treatment with low power red light (e.g. laser) after administration of a photosensitizing drug [14]. There is no increase in tissue temperature and so collagen and elastin are less affected, preserving mechanical properties. Under light illumination at an appropriate wavelength, hydroxy radicals or singlet oxygen are produced inducing oxidation and death of tissues. A wide array of photosensitizers for PDT exists and is marketed.

Conclusion

Many questions remain open in most of the physics-based therapies that we have been shortly reviewed. All are based on principles discovered a long time ago and advances are still far from being sufficient. Clinical studies do not clarify enough how and when they should be used in first intention or sequenced over time. In other words, patients must be cared today and not tomorrow. No doubt that they offer many opportunities. New probe and transducer design, device miniaturization through MEMS technology will converge with the parallel evolution of medical robots, imaging modalities and drug delivery advances. Almost all, if not all, physical therapeutic systems described here are basically image-guided and can be merged into the medical robot frame. Dual sensing and actuating (or activating) devices are in progress, and even if there is a long way from the initial concepts to clinical applications (with inherent quality control and traceability), the trend toward more efficient, less invasive care will support the efforts made in the field. In parallel, basic research opens new windows. For instance, terahertz (THz) imaging (with a frequency range lying between the infrared and microwave regions of the spectrum) is just emerging as a biomedical modality. We do not know if, in the future, it may not have therapeutic applications [15].

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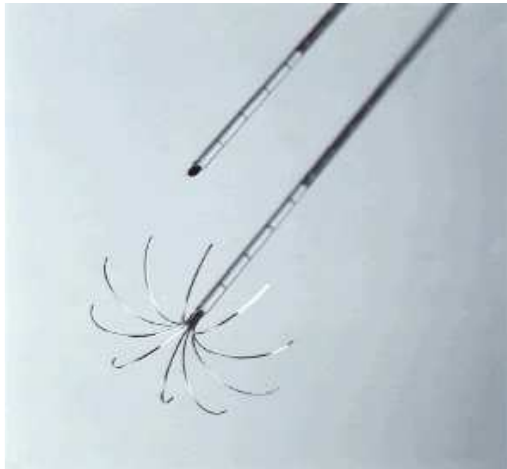


Figure 1. Radiofrequency needle electrode. The gauge needle is introduced into the tumor and then the retractable tines are deployed.

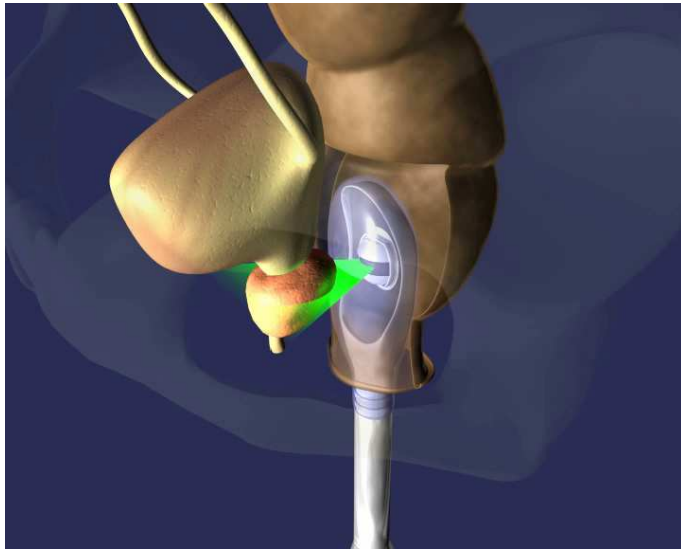


Figure 2. Computer graphics representation of the HiFU transducer for prostate cancer (courtesy EDAP-TMS)

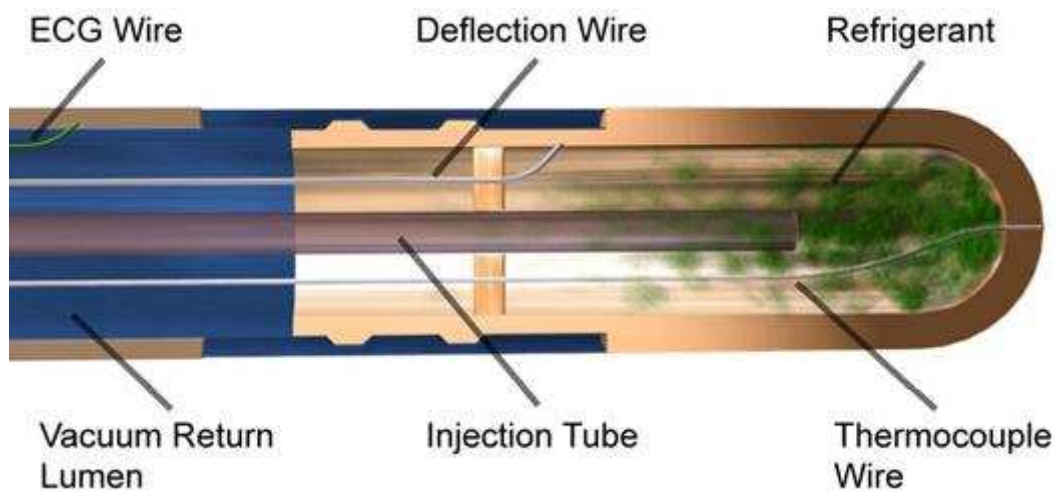


Figure 3. Cryotherapy device. The tip thermocouples offer a temperature feedback that allows controlling the flow of refrigerant delivery (Medtronic & CryoCath).

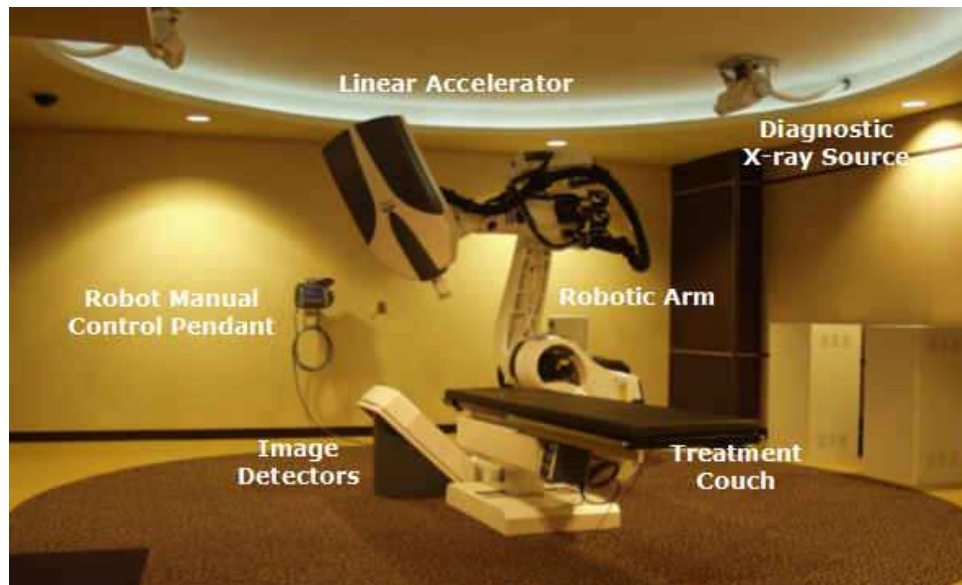


Figure 4. The Cyberknife in the treatment room set-up, based on a Kuka robot (*Accuray Company*).

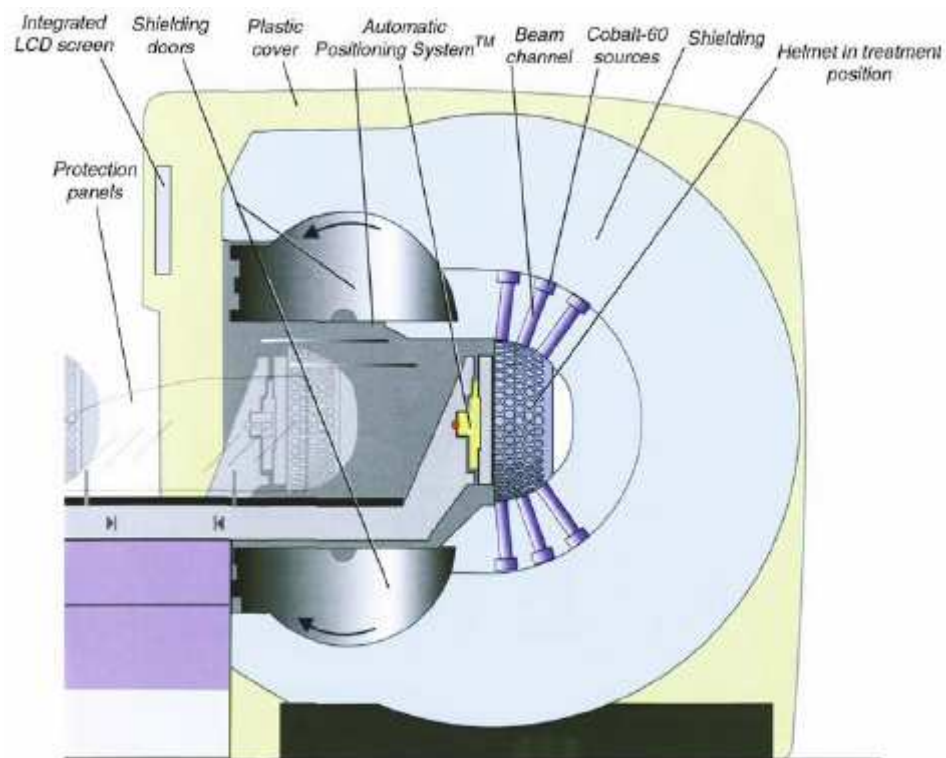
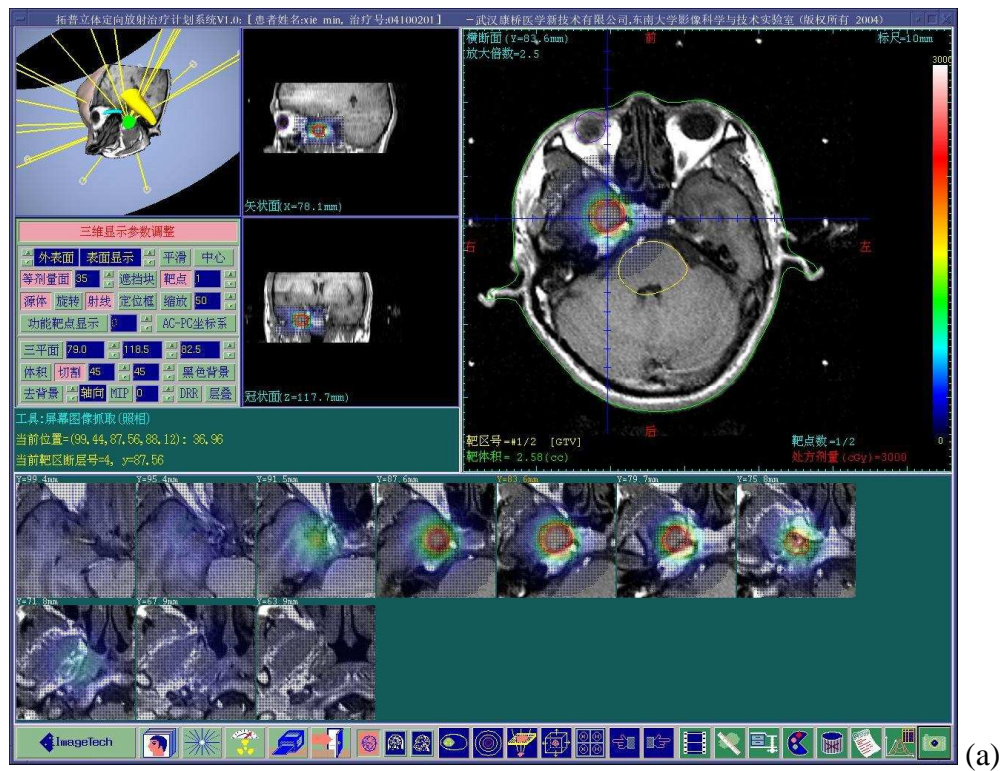
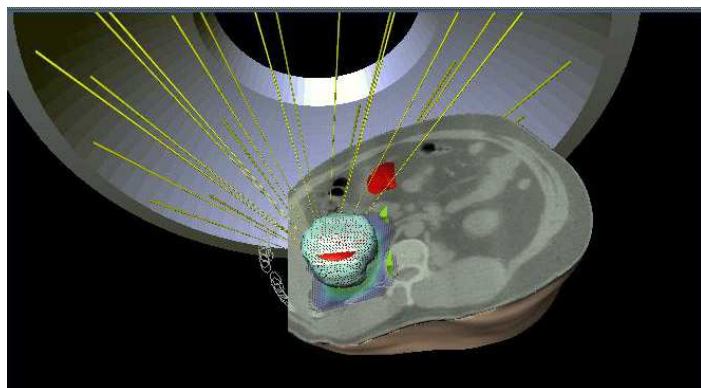


Figure 5. Schematic diagram of the Leksell Gamma Knife 4C (*Elekta*).



(a)



(b)

Figure 6. Illustration of treatment planning and simulation for Rotational Gamma System (LIST, Southeast Univ., China). (a) planning for treatment of a cerebral lesion, (b) simulation for treatment of a abdominal lesion.